herein, claim 35 has been canceled, and claim 73 has been added. No new matter is added to the application by this Amendment. Applicant respectfully requests reexamination and reconsideration of the case. Each of the rejections levied in the Office Action is addressed individually below.

I. **Rejection under 35 U.S.C. § 112, second paragraph, as being indefinite**. Claims 1and 35 have been rejected under 35 U.S.C. § 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which Applicant regards as the invention.

The Examiner states that claims 1 and 35 are indefinite because the phrase "capable of forming" is indefinite as to whether the forming takes place. Applicant respectfully disagrees. To be definite a claim must be definite to one of ordinary skill in the art. Applicant submits that one of ordinary skill in the art would reading claim 1 would find the claim definite. As used in claims 1 and newly added claim 73, the phrase "capable of forming" is used to define the set of atoms represented by X and Z. Examiner says that "the phrase 'capable of forming' renders the claim indefinite as to whether the forming takes place." One of ordinary skill in the art reading claim 1 would understand that the bonding has taken place in the molecule as claimed and that the "capable of forming" merely defines the universe of atoms to which the carbon or nitrogen is singly or doubly bonded. Atoms capable of forming a single bond with carbon include chlorine, bromine, fluorine, iodine, carbon, nitrogen, oxygen, boron, phosphorous, sulfur, *etc.* Applicant, therefore, requests that the rejection be removed since claim 1 is definite to one of skill in this art.

Claim 1 has been amended to recite a "linker moiety" rather than a "linker molecule" and has been reformated for easier reading and clarity as suggested by the Examiner.

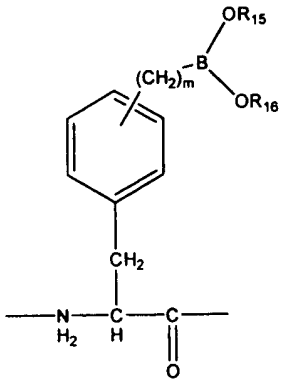
II. **Rejection under 35 U.S.C. § 103, as being unpatentable over Bachovchin (U.S. Patent 5,776,902)**. Claims 1 and 35 have been rejected under 35 U.S.C. § 103, as being unpatentable over Bachovchin (U.S. Patent 5,776,902). The Examiner says that Bachovchin in

U.S. Patent 5,776,902 (the '902 patent) discloses "peptidomimetics which contain one or more moieties that have phenyl boronate sidechains." The Examiner admits that the "reference does not provide the same generic formula" as is found in the present application and does not disclose a specific compound in which there are two boronic ester groups. In the present Application, the claimed chemical compounds are dimers or polymers of peptidomimetics in which the boronic ester group mimics the carboxylate group normally found at the c-terminus of peptides and proteins. Given the substantial structural differences between the compounds disclosed in the '902 patent and the claimed compounds, the Applicant submits that the Examiner has failed to establish a *prima facie* case of obviousness.

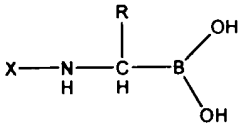
In order to render the claimed invention obvious, the cited reference must teach or suggest to one of ordinary skill in the art every element of the claimed invention. The '902 patent fails to teach or even suggest the compounds claimed in the present Applcation. The '902 patent teaches a peptidomimetic in which the phosphorylated tyrosine residue of the original peptide is replaced with a boro-tyrosine. Essentially the boronate moiety mimics the phosphate group, and the boro-tyrosine represents an amino acid residue in a peptide.

The present application claims peptidomimetics wherein the c-terminus of the peptidomimetic is a boron-containing group. The boron-containing group mimics the carboxylic acid group normally found at the c-terminus of proteins and peptides.

There are several major differences between the compounds disclosed in the '902 patent and the claimed invention. First, the boron-containing group in the '902 patent represents a phosphate group whereas in the claimed invention the boron-containing group represents a carboxylic acid group.



'902 Patent



Present Application

One of ordinary skill in the art reading the '902 patent without further teachings would not be motivated to replace a carboxylic acid group with a boronate ester group.

Second, the boron-containing group is located in the side chain of an amino acid residue of the peptidomimetic of the '902 patent, and in the present application, the boron-containing group is located at the c-terminus of the peptidomimetic. The '902 patent does not teach or suggest the use of a boron-containing group at the c-terminus versus in the side chain of an amino acid residue.

Third, the present application claims a homo- or hetero-dimer or polymer of peptidomimetics with each peptidomimetic ending with a boron-containing group. The '902 patent discloses a peptidomimetic with one or more boro-tyrosine residues and *not* one or more peptidomimetics linked together. As would be appreciated by one of skill in the art, there are substantial structural differences between a dimer or polymer of peptidomimetics and having one or more boro-tyrosine residues in a peptidomimetic.

Given these substantial differences between the '902 patent and the claimed invention, Applicatant submits that the '902 patent does not render the presently claimed invention obvious because the '902 patent does not teach or suggest the elements of the claimed invention in the present application. Applicant respectfully requests that the rejection be removed.

In view of the forgoing arguments, Applicant respectfully submits that the present case is now in condition for allowance. A Notice to that effect is requested.

Please charge any fees that may be required for the processing of this Response, or credit any overpayments, to our Deposit Account No. 03-1721.

Respectfully submitted,

C. Hunter Baker, M.D., Ph.D.
Registration Number: 46,533

Choate, Hall & Stewart
Exchange Place
53 State Street
Boston, MA 02109
(617) 248-5000
Date: January 28, 2002

I hereby certify that this correspondence is being deposited with the United States Postal Service as first class mail in an envelope addressed to: Assistant Commissioner For Patents, Washington, D.C. 20231
on 1/28/02

Appendix A

Version with Markings to Show Changes Made in Specification

1) Marked-up copy of the paragraph on page 18d, line 1:

The invention also embraces compounds which mimic the substrate binding site of other post-prolyl cleaving enzymes. For Example, IgA 1 proteases recognize the cleavage site Ser-Thr-Pro-Pro-X (SEQ ID NO.6), (where X is any amino acid). Accordingly, Ser-Thr-Pro-Pro-R^1 (SEQ ID NO.7), is suitable for selectively binding to, and forming a complex with a functional group in the active site of an IgA 1 protease. The Ser-Thr in this targeting moiety may be readily substituted with any of the 20 naturally occurring amino acids, most preferably those having non-bulky side groups, such as Ala and Gly. It also is possible to substitute non-naturally occurring amino acids, such as 2-azetidinecarboxylic acid or pipecolic acid (which have 6-membered, and 4-membered ring structures respectively) for either of the Pro residues. Those skilled in the art will recognize that there are other such changes which can be made without significantly affecting the binding and complex forming character of these compounds.

2) Marked-up copy of the paragraph on page 18d, line 14:

In the case of IgA 2, protease, the cleavage site in the natural substrate is Pro-Thr-Pro-X (SEQ ID NO.8), with hydrolysis occurring between Pro and X. Thus, a preferred P^1 R^1 binding moiety for binding to an IgA 2 protease has the formula Pro-Thr-Pro-R^1 (SEQ ID NO.9). Thr can be substituted by any of the naturally occurring amino acids, especially ones having non-bulky side groups, such as Ala, Gly or Ser. Other examples of post-prolyl cleaving enzymes which can be targeted by the targeting moieties of the invention include other IgA enzymes, encephalon degrading enzymes, vasopressin degrading enzymes, and oxytocin degrading enzymes.

3) Marked-up copy of the paragraph on page 32, line 10:

2. Heterobivalent Compounds: General Structure

The heterobivalent compounds and agents taught herein may begin with the

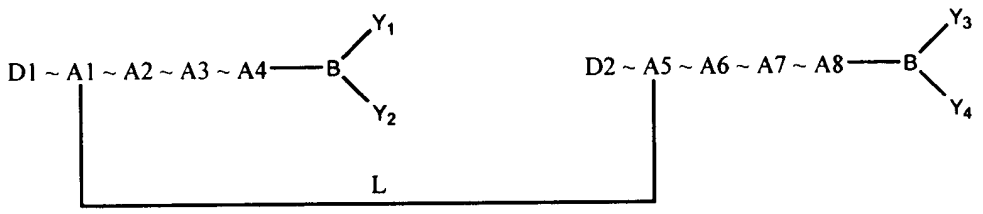
following general diagram as shown in Fig. 2A, the general formula for a heterobivalent compound. Figs. 2A- 2C are diagrams showing the general formula of several preferred heterobivalent compounds: Fig. 2A is a diagram of a general heterobivalent template; Fig. 2B is a diagram of a heterobivalent example coupling a binding moiety to an MCC peptide (94-103) using a compatible linker, e.g., an AAAAAA (SEQ ID NO.1), linker group where A is L-alanine or D-alanine; and Fig. 2C is a diagram of a heterobivalent example coupling a binding moiety to a PLP peptide (139-151) using a comptabile linker, e.g., an AAAAAA (SEQ ID NO.1), linker group where A is L-alanine or D-alanine.

4) Marked-up copy of the paragraph on page 60, line 11:

In the case of PLP, the heteordimer was constructed as HSLGKWLGHPDKFAAAAAA-εKbP (SEQ ID NO.3), where HSLGKWLGHPDKF (SEQ ID NO.2), was PLP 139-151, AAAAAA (SEQ ID NO.1), was a linker comprised of 6 alanines and εKbp was Lysine-boroProline in which the ε-amino of Lysine is covalently attached to the –COOH terminus of HSLGWLGHPDKFAAAAAA (SEQ ID NO.3). The first synthetic step was to order a custom peptide from a synthetic peptide lab. Using long established protocols, the peptide was built from the C-terminus staring with alanine which was immobilized on a resin. Sequentially AAAAAFKDPHGLWKGLSH (SEQ ID NO.4), were added using protected amino acids. The peptide was then removed from the resin to give a free –COOH terminus which could be reacted to form a peptide bond. The other residues HSLGKWLGHPDKFAAAAA (SEQ ID NO.5), were unreactive owing to protecting groups. Lysine-boroProline in which the α-NH_2 of Lysine was protected, the $B(OH)_2$ of boro Proline was protected with pinanediol, and the ε-NH_2 of Lysine was free was coupled to the peptide. The coupling was a peptide bond (-(C=0)–NH-) formed by standard peptide chemistry techniques. The result was then deprotected to yield the final product.

Appendix B

1. (Amended) A compound, having the structure



wherein D1 and D2, independently, are selected from the group consisting of NH and NH_2,

wherein N represents any isotope of nitrogen,

wherein H represents any isotope of hydrogen;

"~", independently, is selected from the group consisting of a single bond and a double bond;

B represents, independently, any isotope of boron;

A1 and A5 are, independently, selected from a group consisting of a C, a CX moiety and an N,

wherein C represents any isotope of carbon,

wherein X represents any atom capable of forming a single bond with C;

each A2, A3, A4, A6, A7, and A8 are, independently, selected from a group consisting of a CX moiety, a CXZ moiety, a CZ moiety, an NX moiety, and an O,

wherein X and Z, are, independently, selected from the groups consisting of any atom capable of forming a single bond and any atom capable of forming a double bond with C or N and wherein O represents any isotope of oxygen;

wherein each Y1, Y2, Y3, and Y4 are, independently, selected from the group consisting of hydroxyl moiety and any reactive moiety that converts to a hydroxyl group moiety under physiologic conditions; and

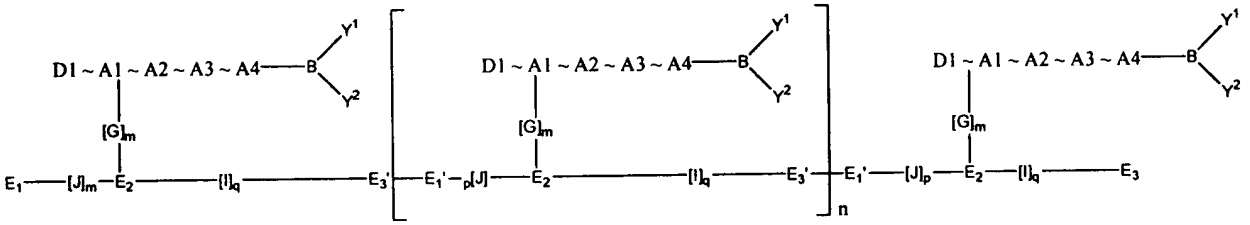
L represents a linker moiety

(i) having a molecular weight ranging between about 100 daltons and about 2000 daltons,

(ii) having a span ranging from about 20 Å to about 300 Å, and

(iii) containing a chain of atoms selected from the group consisting of a combination of C, O, N, S, and P atoms, connected by single bonds or by double bonds in a manner that does not violate the laws of chemistry and wherein S represents any isotope of sulfur and P represents any isotope of phosphorous.

73. A compound, having the structure



wherein D is, independently, selected from the group consisting of NH and NH_2,

wherein N represents any isotope of nitrogen,

wherein H represents any isotope of hydrogen;

"~", independently, is selected from the group consisting of a single bond and a double bond;

B represents, independently, any isotope of boron;

A1 is, independently, selected from the group consisting of a C, a CX moiety, and an N,

wherein C represents any isotope of carbon,

wherein X represents any atom capable of forming a single bond with C;

each A2, A3, and A4 are, independently, selected from the group consisting of a CX moiety, a CXZ moiety, a CZ moiety, an NX moiety, and an O,

wherein X and Z, independently, are selected from the group consisting of any atom capable of forming a single bond and any atom capable of forming a double bond with C or N and wherein O represents any isotope of oxygen;

wherein Y1 and Y2 are, independently, selected from the group consisting of a hydroxyl moiety and any reactive moiety that converts to a hydroxyl group moiety under physiological conditions;

n represents an integer between 1 and 200, inclusive;

wherein E1 and E3 are independently selected from the group consisting of a carboxylate, amino, imidazole, sulfhydryl, aldehyde, ester, amide, acid chloride, carbonate, and carbamate group such that the E1 and E3 are capable of reacting and forming an –E1'—E3'— adduct with a covalent bond between E1' and E3';

wherein $[J]_p$, $[I]_q$, and $[G]_m$ together comprise a linker moiety, and wherein $[G]_m$, $[J]_p$, and $[I]_q$ represent, independently, a linker group (i) having a molecular weight ranging between about 100 daltons and about 2000 daltons, (ii) having a span ranging from about 20 Å to about 300 Å, and (iii) containing a chain of atoms selected from the group consisting of a combination of C, O, N, S, and P atoms, connected by single bonds, double bonds, or triple bonds in a manner that does not violate the laws of chemistry and wherein S represents any isotope of sulfur and P represents any isotope of phosphorus; and wherein m, p, and q represent, independently, an integer from 1 to 50, inclusive;

E2 is selected from the group consisting of CX, CH, N, PYZ, PU, and B such that E2 is capable of forming a covalent bond with $[J]_p$, $[G]_m$, and $[I]_q$ and

wherein C is any isotope of carbon;

X is, independently, selected from the group consisting of any atom capable of forming a single bond with carbon;

Y is, independently, selected from the group consisting of any atom capable of forming a single bond with phosphorous;

Z is, independently, selected from the group consisting of any atom capable of forming a single bond with phosphorous;

H is any isotope of hydrogen;

N is any isotope of nitrogen;

P is any isotope of phosphorus;

B is an isotope of boron;

U is, independently, selected from the group consisting of any atom capable of forming a double bond with phosphorous.